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Good agreement between echocardiography and impedance cardiography in the assessment of left ventricular performance in hypertensive patients

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ABSTRACT

Background: Impedance cardiography (ICG) is a noninvasive hemodynamic monitoring tool which can define hypertensive patients' hemodynamic profiles and help to tailor antihypertensive therapy. This study assesses the concordance between ICG-derived indexes used to evaluate left ventricular performance and transthoracic echocardiography (TTE) in hypertensive patients. *Methods*: In this IMPEDDANS *post-hoc* analysis, the ICG-derived indexes are compared with TTE by Bland–Altman method. Statistical significance of the relationship between the values obtained was assessed by generalized linear mixed-effects models. *Results*: In supine position, Bland–Altman analysis showed good concordance for cardiac output (CO) (mean difference of 0.006 mL/min [−0.120; 0.133]), cardiac index (CI) (mean difference of 0.016 mL/min/m^2 [−0.471; 0.504]), pre-ejection period (PEP) (mean difference of −0.216 ms [−4.510; 4.077]), left ventricular ejection time (LVET) (mean difference of −0.140 ms [−6.573; 6.293]), and systolic time ratio (STR) (mean difference of −0.00004 [−0.008; 0.008]). In orthostatic position, good concordance was found for CO (mean difference 0.028 mL/min [−2.036; 1.980]), CI (mean difference −0.012 mL/min/m^2 [−1.063; 1.039]), and STR (mean difference −0.101 [0.296; 0.094]). No significant difference between methods was identified by the linear mixed-effects models. *Conclusion*: The ICG-derived indexes CO, CI, PEP, LVET, and STR in supine position have good agreement with TTE. Therefore, ICG can be used to accurately evaluate left ventricular performance.

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Echocardiography; impedance cardiography; hypertension; left ventricular performance; systolic time intervals

Background

Impedance cardiography (ICG) has evolved in recent years, it is already used in several setting (e.g., evaluation of postural cardiac rehabilitation, pacemaker optimization, sleep study, hemodynamic monitoring in pregnancy and in the outpatient setting), and it has become an attractive and economical alternative to the clinical approach to hypertensive patients (1–7). ICG is a noninvasive hemodynamic monitoring tool, nonoperator dependent and non-expensive, which can characterize hemodynamic profiles and contribute to optimize antihypertensive therapy (8,9). The use of ICG hemodynamic parameters has been proposed to guide pharmacologic prescription according to the pathophysiological mechanism involved in the sustained elevation of blood pressure (BP) (10–15). This personalized, guided hemodynamic therapy approach reveals both efficacy and cost-effectivity (10–15).

The evolution of hypertensive heart disease toward heart failure (HF) involves structural and geometry modifications which can impair left ventricular (LV) function (9,16). Recent reports suggest that the ICG-derived systolic time intervals may be used to monitor impaired systolic and/or diastolic LV function; however, there are conflicting results concerning the screening of LV impairment and in the validation of the ICG-derived indexes. Therefore, it is necessary to validate the method in specific clinical settings (17–25). This study verifies the agreement between ICG-derived indexes used in evaluating LV function and the clinical standard, in patients with severe hypertension (HT).

Methods

Study design

In this *post-hoc* analysis of data from the IMPEDDANS project (Impedance Cardiography in the Evaluation of Left Ventricular Diastolic dysfunction in Patients with Arterial Hypertension Study), the ICG-derived indexes are compared with contemporary transthoracic echocardiography (TTE)-derived indexes, used nowadays as the clinical standard. The cardiac output (CO), cardiac index (CI), pre-ejection period

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Supplemental data for this article can be accessed here.

(PEP), left ventricular ejection time (LVET), and systolic time ratio (STR) are assessed by ICG (in supine and orthostatic positions) and TTE. The project protocol was approved by the hospital's Ethics Committee (approval number 166/2014). Informed consent was obtained from each patient. IMPEDDANS is registered on ClinicalTrials.gov (ID: NCT03209141).

Sampling

Patients of either gender, aged 18–75 years, with grade 2 or 3 HT (systolic BP ≥ 160 mmHg and/or diastolic BP ≥ 100 mmHg) and/or with resistant HT (according the definition of ESH/ESC guidelines) (26), followed up in ambulatory clinic of an Internal Medicine Department of a tertiary referral hospital were eligible for recruitment.

Patients were excluded in the presence of pregnancy, height <120 cm or >230 cm, weight <30 kg or >155 kg, HF II–IV NYHA (27), heart rate (HR) <50 bpm or >110 bpm, atrial fibrillation or flutter, more than three premature ventricular contractions per hour, complete left bundle branch or atrioventricular block, pacemaker, severe valvulopathy, constrictive pericarditis, hypertrophic and restrictive cardiomyopathy, ischemic heart disease and/or segmental kinetics anomalies assessed by echocardiography, left ejection fraction <50%, or poor echocardiographic window. Recruitment began in January 2015 and was finished in July 2017.

Evaluations and data collection

Participants were invited to be systematically assessed by ICG and echocardiography, with a maximum interval of 8 days in between. To ensure that both tests were performed under similar conditions, evaluations matching variations >10% in BP or variations >5% in HR were not considered. These patients were asked to repeat the tests. If the variations persisted, they were excluded.

ICG was carried out by an experienced cardiopneumology technician with Niccomo – Non-Invasive Continuous Cardiac Output Monitor (Medis GmbH, Ilmenau, Germany) – according the approved department protocol. Patients were required to have 6 h of fasting but took their usual antihypertensive drugs. With patients in dorsal decubitus, it was carried out in supine position during 20 min (continuous recording) and 70° orthostatism on a tilting table (10 min in continuous recording). The test was interrupted whenever occurred syncope or pre-syncope; dizziness, nausea, and malaise associated with poorly tolerated hypotension and/or bradycardia; pain/precordial discomfort; EKG ST segment changes; systolic BP >210 mmHg.

TTE was performed in Vivid E9 and S5 devices (GE Healthcare, Chicago, IL, USA) always by experienced cardiologists. To ensure uniformity of evaluation and correct evaluation, all exams were reviewed by another independent cardiologist. The exam was performed with the patients in left lateral decubitus. CO was calculated based on measurement of the flow velocity time integral (VTI) measured over the aortic valve (AoV), measured from an apical four-chamber view with angle correction, if necessary, multiplied by the area of the AoV:CO = AoV area × VTI × HR, where the AoV diameter was determined by triplicate measurements of the internal diameter of the AoV hinge points: AoV area = $(0.5 \times \text{diameter})^2 \times 3.14$ (28). LVET (ms) was measured as the duration of flow using standard pulsed wave Doppler with sample volume in the LV outflow tract just below the AoV leaflets. PEP (ms) was measured as the time interval between R wave on ECG and beginning of LV outflow tract flow. The ratio of PEP to LVET was also obtained (29).

The correlation between the parameters obtained by ICG (both in supine and orthostatic positions) and TTE was assessed by Spearman correlation test; the strength of correlation was interpreted according to Hinkle et al (30). To evaluate the agreement between ICG (both in supine and orthostatic positions) and TTE for measuring CO, CI, PEP, LVET, and STR, Bland–Altman method was used. Additionally, the statistical significance of the relationship between the values obtained by ICG and TTE was assessed using generalized linear mixed-effects models. The level of significance $\alpha = 0.05$ was considered. Data were analyzed with Stata 11.0 (StataCorp. 2011, Stata Statistical Software: Release 12. College Station, TX: StataCorp LP).

Results

IMPEDDANS study recruited 167 patients. Ten patients were excluded: three had syncope during ICG, three gave up and did not perform the tests, three had a significant dysrhythmia, and one was diagnosed as having an atrial septal defect. From the 157 hypertensive patients included, 102 (65%) had LV diastolic dysfunction (diagnosed by echocardiogram). Table 1 shows the main demographic and clinical characteristics of the patients.

The values obtained by ICG (in both supine and orthostatic positions) and by TTE are presented in Table 1. The values of every parameter obtained by ICG in supine position had a very high correlation with their equivalents obtained by TTE; on the other hand, the TTE-derived parameters had low or moderate correlation with the values obtained by ICG in orthostatic position (Table 2 and Supplementary Figure 1).

Table 1. Main characteristics of the effective sample (n = 157).

Males, *n* (%)	88 (56.1)
Age, mean (SD)	63 (10)
Caucasian, *n* (%)	142 (90.4)
HT duration (months), mean (SD)	120 (104)
Resistant HT, *n* (%)	117 (74.5)
Obesity, *n* (%)	82 (52.2)
Diabetes mellitus, *n* (%)	81 (51.6)
Dyslipidemia, *n* (%)	133 (84.7)
CKD, *n* (%)	49 (31.2)
Stroke, *n* (%)	36 (22.9)
COPD, *n* (%)	20 (12.7)
OSA, *n* (%)	31 (19.7)
Smoker, *n* (%)	34 (21.7)
Alcoholic, *n* (%)	16 (10.8)
No. of AHT drugs, median (min–max)	4 (1–7)

AHT: Antihypertensive; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; HT: hypertension.

Table 2. Cardiac output, cardiac index, pre-ejection period, left ventricular ejection time, and systolic time ratio obtained by ICG (in supine [s] and orthostatic [o] positions) and by transthoracic echocardiography values.

	ICGs	ICGo	TTE	Correlation TTE:ICGs (r)	Correlation TTE:ICGo (r)
CO (mL/min), median (P_{25}–P_{75})	5.2 (4.3–6.0)	5.3 (4.5–6.0)	5.2 (4.4–6.0)	0.998	0.577
CI (mL/min/m^2), median (P_{25}–P_{75})	2.7 (2.4–3.5)	2.8 (2.5–3.1)	2.7 (2.4–3.1)	0.996	0.437
PEP (ms), median (P_{25}–P_{75})	93 (79–105)	117 (99–133)	93 (79–104)	0.991	0.533
LVET (ms), median (P_{25}–P_{75})	332 (291–369)	307 (268–332)	330 (292–369)	0.997	0.491
STR, median (P_{25}–P_{75})	0.28 (0.24–0.33)	0.39 (0.32–0.46)	0.28 (0.24–0.33)	0.996	0.455

CI: Cardiac index; CO: cardiac output; LVET: left ventricular ejection time; PEP: pre-ejection period; STR: systolic time ratio; TTE: transthoracic echocardiography. Correlations calculated with Spearman index (*r*).

The Bland–Altman analysis showed a good concordance between the values of the parameters obtained by TTE and by ICG in supine position (Figure 1(a–e)): for CO, the mean difference was 0.006 mL/min (limits of agreement −0.120–0.133); for CI, mean difference 0.016 mL/min/m^2 (−0.471–0.504); for PEP, mean difference −0.216 ms (−4.510–4.077); LVET, mean difference −0.140 ms (−6.573–6.293); and STR, mean difference −0.00004 (−0.008–0.008).

The Bland–Altman analysis of the values of the parameters obtained by TTE and by ICG in orthostatic position (Figure 1(f–j)) showed good concordance for CO (mean difference 0.028 mL/min; limits of agreement −2.036–1.980) and CI (mean difference −0.012 mL/min/m^2; limits of agreement −1.063–1.039). The agreement was worse for PEP (mean difference −22.649 ms; limits of agreement −66.316–21.017), LVET (mean difference of 25.617 ms; limits of agreement −73.194–124.429), and STR (mean difference −0.101; limits of agreement −0.296–0.094).

The linear mixed effects models identified no significant difference between the TTE-derived values and those obtained by ICG performed in supine position, in any of the parameters ($p = 0.214$–0.890). For the parameters obtained by ICG performed in orthostatic position, a significant difference to the TTE-derived values was found for PEP, LVET, and STR ($p < 0.001$) (Table 3).

Discussion

This study found good agreement (Bland–Altman analysis) between the TTE-derived parameters (CO, CI, PEP, LVET, STR) and those ICG-derived evaluated in supine position. The agreement of TTE-derived parameters and those ICG-derived evaluated in orthostatic position was acceptable for CO and CI but low for PEP, LVET, and STR. These results demonstrate that the ICG in supine position can be used as a reliable and cost-effective alternative for evaluation and monitoring LV performance-derived indexes.

The good agreement found between these two methods may help to reduce doubts about the usefulness of ICG in hypertensive patients. Although there are many published articles about the benefits of ICG and its applicability, there are issues that have conditioned its overall use. Most studies carried out had small samples, the accuracy and reproducibility of each variable was differently determined between trials, and results were conflicting (25). TTE has rarely been used as a reference method to analyze the agreement of the parameters evaluated by ICG and studies presented different results with correlation coefficients ranging from 0.27 to 0.95 (25,31–35).

There are few studies that evaluate the concordance of other parameters besides CO (25). In literature, we find three meta-analysis that group almost all studies that compare the agreement of CO evaluated by ICG with other reference methods. Fuller et al. analyzed 28 studies comparing ICG with the Fick and thermodilution methods and concluded that ICG had a correlation coefficient of 0.81 (36). Raaijmakers et al., in a meta-analysis of 112 studies, determined a correlation coefficient of 0.82 (37). Recently, Peyton and colleagues conducted a new meta-analysis of studies comparing ICG, esophageal Doppler, pulse-wave contour analysis, and the Fick method with thermodilution (38). These authors report a correlation coefficient of 0.79 and low mean difference for ICG revealing better agreement than the other noninvasive methods (38).

Despite these favorable results, some studies have shown a low correlation between ICG and the various methods of hemodynamic evaluation, namely in obese patients, in patients with HF, chronic obstructive pulmonary disease, aortic valvulopathy, dysrhythmia, in septic patients, under mechanical ventilation, post cardiac surgery, among others (39–43). Signal interference, hardware problems that impaired signal sensitivity, or even the incorrect placement of the electrodes are also potential biases in the ICG evaluations (44–46). The technological developments that have been introduced proved to be effective in their resolution, and trials conducted with newer monitors have shown good agreement with other methods (43,47).

Thus, we attribute the good agreement found in this study, with correlation coefficients higher than the global values found in the previous studies ($r = 0.99$) and with low mean differences and agreement limits, to the fact that we excluded factors that influence the evaluations by ICG such as the presence of HF, significant valvulopathy, moderate-to-severe chronic obstructive pulmonary disease, dysrhythmias, among others comorbidities which could bias the evaluations; we included only ambulatory patients; we used a new generation monitor; we performed both examinations according to an well-defined protocol and in a controlled clinical setting, by expert practitioners.

Furthermore, previous studies report good reproducibility of the evaluations performed on the same day but only acceptable reproducibility when performed on different days ($r = 0.65$–0.86) (48–50). The fact that our protocol establishes that the examinations had to be performed in a short period of time (8 days) and that patients could not present variations

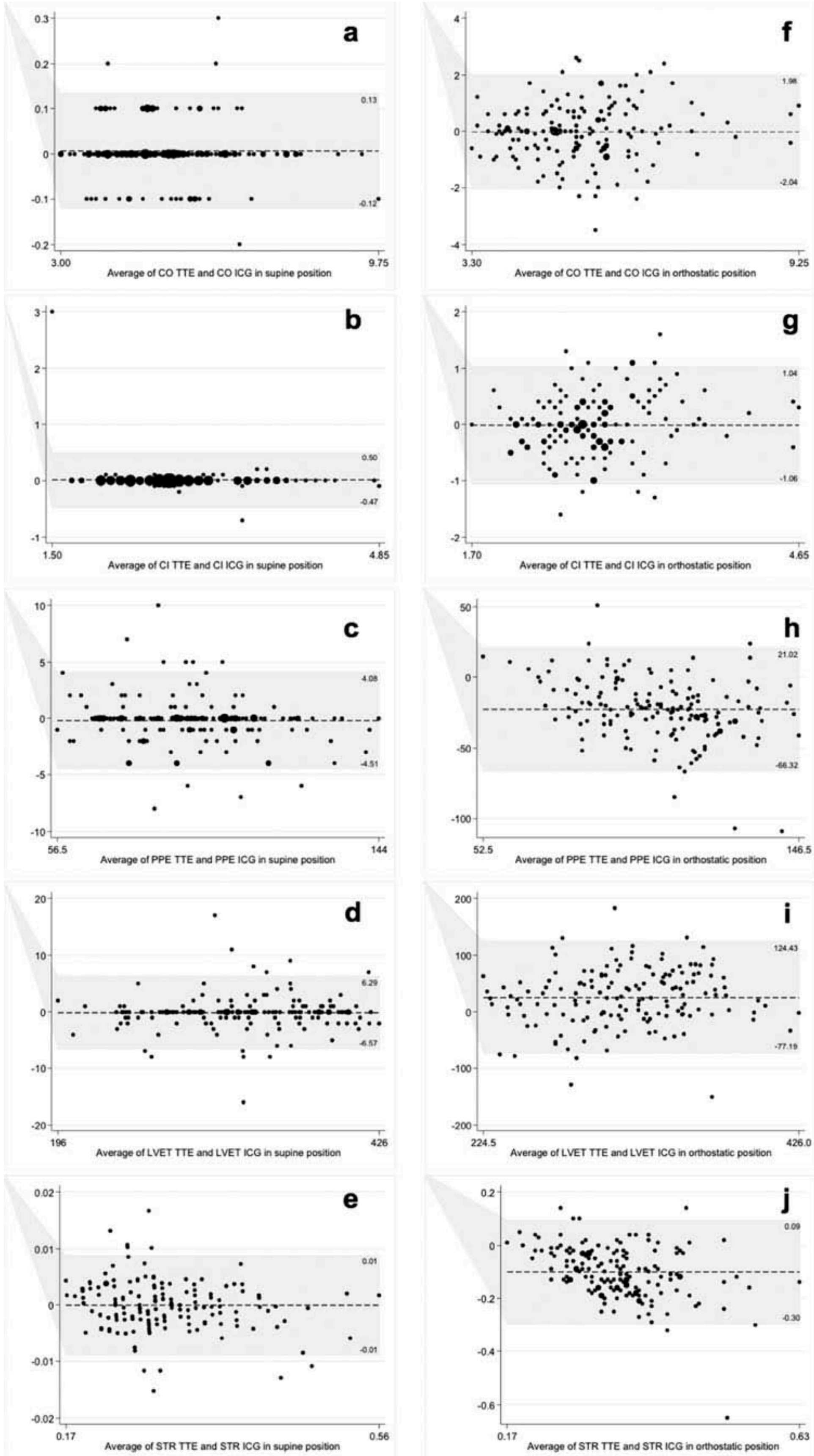

Figure 1. Agreement of the indexes used to evaluate left ventricular performance obtained by TTE and by ICG, both in supine and orthostatic positions. (a) Cardiac output in supine position, (b) cardiac index in supine position, (c) pre-ejection period in supine position, (d) left ventricular ejection time in supine position, (e) systolic time ratio in supine position, (f) cardiac output in orthostatic position, (g) cardiac index in orthostatic position, (h) pre-ejection period in orthostatic position, (i) left ventricular ejection time in orthostatic position, and (j) systolic time ratio in orthostatic position.

CI: Cardiac index; CO: cardiac output; ICG: impedance cardiography; LVET: left ventricular ejection time; PPE: pre-ejection period; STR: systolic time ratio; TTE: transthoracic echocardiography.

Table 3. Relationship between the values of the parameters used to evaluate left ventricular performance obtained by ICG (supine and orthostatic positions) and TTE was performed by regression analysis using generalized linear mixed effects models.

	Coefficient estimate (95% CI)	*p* Value	Coefficient estimate (95% CI)	*p* Value
Parameter	ICG in supine		ICG in orthostatic	
CO	−0.01 (−0.016; 0.004)	0.216	0.03 (−0.132; 0.188)	0.731
CI	−0.02 (−0.055; 0.022)	0.403	0.12 (−0.072; 0.096)	0.777
PEP	0.22 (−0.125; 0.558)	0.214	22.65 (19.176; 26.124)	<0.001
LVET	0.14 (−0.371; 0.651)	0.592	−25.62 (−33.479; −17.757)	<0.001
STR	0.00 (−0.001; 0.001)	0.890	0.10 (−0.086; 0.117)	<0.001

95% CI: 95% Confidence interval; CI: cardiac index; CO: cardiac output; ICG: impedance cardiography; LVET: left ventricular ejection time; PEP: pre-ejection period; STR: systolic time ratio; TTE: transthoracic echocardiography.
TTE is the reference category.

greater than 5% in HR and 10% in BP, by minimizing hemodynamic variability, may also have contributed to this good agreement between methods.

The evaluation of the hemodynamic response to postural change from supine to upright position provides useful information on the cardiovascular reflex activity (51). The change from supine to orthostatic position in healthy individuals provokes reduction in thoracic blood volume and stroke volume with subsequent decrease pressure on carotid baroreceptors which then causes a rise in HR and posterior sympathetic vasoconstriction with BP normalization. Associated to the high HR, the systolic time intervals usually decrease (52,53).

Most of the studies were designed to study syncope and therefore differences in orthostatic hemodynamics have not been truly explored among hypertensive patients (54). It was found that age was a major determinant of the response to orthostatism, as those with stable stroke volume and CO were mostly older hypertensive patients eventually related with impaired carotid baroreflex or impaired autonomic balance between arterial and cardiopulmonary baroreflexes (51).

The sample in the present study has many resistant, polymedicated, hypertensive patients with multiple comorbidities, such as diabetes mellitus, which may affect the hemodynamic response to orthostatism. This may contribute to the great dispersion detected for ICG-derived indexes (PEP, LVET, STR) and may explain the poor agreement between ICG-derived indexes in orthostatic position and those obtained by TTE, which is performed in supine position.

Echocardiographic measures of LV structure, morphology, and function still continue to be important in the evaluation of heart damage in hypertension (26). However, the significant differences found between ICG-derived indexes in supine/orthostatic position and TTE evaluations indicate that the individual analysis of hypertensive patients with ICG in both positions may add information about the patients' pathophysiological response, improving their hemodynamic characterization and therapeutic optimization.

Future studies in the area of ICG may increase our understanding of the pathophysiology and hemodynamic changes of arterial hypertension, in particular the importance of postural variability, and evidence that early diagnosis and treatment of these hemodynamic characteristics have a positive impact on patient outcomes, reducing morbidity and mortality associated with arterial hypertension.

This study had some limitations. This is a concordance analysis, not strictly a validation study, as the ICG-derived parameters are compared with TTE-derived parameters, which is not the gold standard, but the current clinical standard. It is a *post-hoc* analysis, based on data obtained for a study whose sample size was intended to reach a different goal. ICG and TTE were performed not simultaneously but within a time lapse of 8 days, a period during which the patients were assumed to remain clinically stable, without any changes of therapy. In order to minimize these weaknesses, a special effort was paid to guarantee the validity of the measurements. Sampling had strict inclusion and exclusion criteria; patients were submitted to the same well-defined evaluation protocols, performed in a controlled clinical environment by experienced professionals. Moreover, evaluations matching variations >10% in BP or variations >5% in HR were not considered.

Conclusions

There is strong evidence that ICG performed in supine position can accurately evaluate LV performance in hypertensive patients, as ICG-derived systolic time intervals, CO, and CI have good agreement with the parameters obtained by the clinical standard (TTE).

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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